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## **The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma**

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## POINT/COUNTERPOINT

The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma

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To estimate the value of whole brain radiotherapy (WBRT) in the treatment of primary CNS lymphoma (PCNSL), it is important to recall the goals of treatment when confronted with this disease: presumably, our common goals of PCNSL treatment include: to improve neurological deficits, to improve or maintain quality of life, to delay neurological progression, to prolong progression-free survival, to prolong overall survival, and eventually to achieve a cure.

Very few of these goals are achieved with WBRT in the current landscape of improved systemic therapy options for PCNSL. Historically, it had been recognized that PCNSL is less sensitive to irradiation than lymphomas elsewhere in the organism and might therefore potentially require higher doses to achieve local control. Accordingly, Radiation Therapy Oncology Group (RTOG) study 8315 explored whether treating the whole brain at 40 Gy and increasing the tumor dose to

60 Gy would result in improved outcome. In fact, median overall survival was only 11.6 months from the start of radiotherapy; 16 of 26 patients with post-treatment CT scans were considered to have a complete response, a finding commonly cited to demonstrate the efficacy of RT in that disease. Importantly, however, these 16 patients represent a highly selected population because patients who progressed during radiotherapy were not included here.<sup>1</sup>

With the introduction of high-dose methotrexate into the first-line treatment of PCNSL, the survival outcome was greatly improved, establishing initial chemotherapy containing high-dose methotrexate as a new standard of care, superiority of which, e.g., over RT alone, was never formally demonstrated in a randomized clinical trial. However, it became also soon apparent that the encouraging activity of combined modality treatment came at a high price. There was a major risk of severe neurotoxicity in surviving patients with a dramatic increase of risk in the elderly.<sup>2</sup> The association of the administration of WBRT and delayed neurotoxicity defined by cognitive decline and characteristic changes on neuroimaging has been confirmed repeatedly ever since.<sup>3,4</sup> Accordingly, the increasing awareness that the administration of WBRT was probably incompatible with long-term survival with adequate quality of life resulted in numerous approaches to treat PCNSL with systemic chemotherapy or combined systemic and intraventricular chemotherapy alone.<sup>5-9</sup> Yet, although retrospective analysis had failed to support a role for WBRT in prolonging overall survival many years ago,<sup>10</sup> clinical practice did not respond and WBRT continued to be used at many sites throughout the world, even in the first-line setting. Thus, it was stated that the formal demonstration that WBRT could be omitted from the first-line treatment of PCNSL without compromising overall survival required a randomized clinical trial. This major endeavor was eventually agreed upon with the formation of the German PCNSL Study Group in the late nineties and took

until 2009 to complete enrolment. Patients with histologically confirmed PCNSL were to receive initial high-dose methotrexate chemotherapy, as monotherapy until 2005 and in combination with ifosfamide thereafter, as initial treatment. Patients who achieved a complete response were then treated with consolidating WBRT or observation alone, based on a randomization done prior to induction chemotherapy. Patients without a complete response were to be treated per initial randomization with WBRT or high-dose cytarabine. The latter was considered the best alternative systemic treatment at the time the trial was designed. The initial report of the primary outcome measures<sup>11</sup> as well as the final report<sup>12</sup> indicate that the omission of WBRT from the initial treatment does not compromise survival whichever way the data are explored, including various subgroup analyses.

Given the current dichotomy of PCNSL treatment of aiming for cure in young (fit) patients as opposed to maintaining remission in old (frail) patients,<sup>13</sup> it becomes apparent that there is indeed no more role for WBRT in the initial treatment of the disease. If we want to cure young patients we cannot take the risk of inducing cognitive impairment for their remaining lifetime. In the elderly where we aim for maintaining the remissions we achieve, we should not use WBRT because of the strongly increased sensitivity of elderly patients to treatment-associated neurotoxicity. In light of the absence of a survival benefit for standard dose radiotherapy (30 x 1,5 Gy) in the G-PCNSL-SG-1 trial,<sup>11,12</sup> the rationale of using a lower dose of WBRT, e.g. 13 x 1.8 Gy,<sup>14</sup> in this setting remains doubtful.

This leaves us with the consideration of whether PCNSL should be treated with WBRT at recurrence. A retrospective study of 48 patients treated with salvage WBRT reported a complete response rate of 58% and a partial response rate of 21%, and median survival from initiation of WBRT was 16 months.<sup>15</sup> While these data may be cited to support the role of WBRT in recurrent PCNSL, randomized data are again

more compelling and are in fact available looking into the G-PCNSL-SG1 trial.

Activity of WBRT as a salvage treatment was demonstrated for progression-free survival, but even here not for overall survival,<sup>11</sup> and the quality of post-progression survival with *versus* without WBRT remains to be explored.

Overall, these data available in the public domain allow to formulate some hypotheses on the treatment of PCNSL as summarized in the Table, and I would be hesitant to randomize either young or fit patients, or elderly or unfit patients, for a trial containing WBRT at any dose.

Is there no role for RT in this disease at all? Only prospective trials can support the claim that WBRT with hippocampal sparing is safer than standard WBRT, and this would only address the safety concern, not the efficacy concern. Could there be a role for focused RT e.g. in partial responders or to consolidate remission? Traditional views say “no”, but traditional views also said that there was no role for surgery until it was looked at in a reasonably sized patient population for the first time.<sup>16</sup>

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**Table. Key conclusions**

- There is no safe dose of WBRT for the brain
- Reduced dose WBRT will not be more effective than standard dose WBRT
- Intensifying chemotherapy up-front will not make WBRT for consolidation more effective
- Intensifying chemotherapy up-front will not make WBRT for consolidation safer

- PCNSL needs to be „cured“ up-front, not at recurrence: WBRT at recurrence remains an option, but probably does not prolong survival